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Association between IRGM polymorphisms and tuberculosis risk

A meta-analysis

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Abstract

Background: The human immunity-related GTPase M (IRGM) is involved in regulating autophagy against invading pathogens. Recently, inconsistent results have been reported about the association between IRGM polymorphisms and tuberculosis risk in several studies.

Methods: We searched the PubMed, Embase, and Web of Knowledge, and extracted data from eligible articles to estimate the associations between IRGM polymorphisms (rs10065172, rs4958842, rs4859843, rs4859846, and rs72553867) and tuberculosis risk. The pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated using Review manager 5.3. The studies heterogeneity was assessed by Cochran Q test. Funnel plot, Begg test, and Egger linear regression test were used to evaluate the publication bias.

Results: Nine case-control studies in 8 articles involving 3780 tuberculosis and 4835 control were analyzed. The analysis showed that IRGM rs10065172 and rs4859846 were significantly associated with tuberculosis risk in all genetic models whereas the latent tuberculosis infection group in 1 study was excluded. However, stratified analysis revealed significant associations for IRGM rs10065172 in all genetic models among Asians, but not for African/African-Americans. Significant associations were observed in recessive and dominant model for rs4958842, allele and recessive model for rs4859843, and all genetic models for rs4859846. No significant associations between rs72553867 polymorphism and tuberculosis risk was identified. Publication bias was detected in allele and additive model of rs4859843.

Conclusions: IRGM rs10065172 was associated with decreased risk of tuberculosis in Asian populations, but not in African/Africa-Americans. rs4958842, rs4859843, and rs4859846, had a large protective effect in Asians, whereas rs72553867 was not associated with tuberculosis risk.

Abbreviations: CI = confidence intervals, HWE = Hardy-Weinberg equilibrium, IRGM = immunity-related GTPase M, kb = kilobases, LTBI = latent tuberculosis infection, Mtb = *Mycobacterium tuberculosis*, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, TB = tuberculosis.

Keywords: immunity-related GTPase M, meta-analysis, polymorphism, tuberculosis

1. Introduction

Tuberculosis, caused by *Mycobacterium tuberculosis* (Mtb), remains a major cause of death around the world especially in developing countries. In 2015, there was an estimated 10.4 million new TB cases worldwide. Of all TB cases worldwide, 60% occurred in just 6 countries, including India, China, Indonesia, Pakistan, Nigeria, and South Africa.[1] Actually, the risk of developing active disease is estimated to be approximately 10% in those individuals infected by Mtb,[2] indicating that host factors play an important role in disease susceptibility and development.

Mtb is an intracellular pathogen which can prevent phagosome-lysosome fusion,[3] and regulate the autophagy pathway

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HX and CL equally contributed to the manuscript, and should be considered as the co-first author. HX and CL contributed to the conceptualization of the study. NZ and LC supervised the study. HX, MZ, and CL performed the experiments. HX, MZ, and CL analyzed the data. HX and CL drafted the manuscript.

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for its own survival, thus reside and replicate within host-derived phagosome in infected macrophages.[4] Susceptibility to TB is partly genetically determined, and variations in genes involved in the autonomous immunity pathway may affect the host response to Mtb infection. For example, autophagy physically removes damaged components through lysosome to promote protein turnover, and serves as an autonomous immunity to eliminate invading pathogens.[6] Human immunity-related GTPase M (IRGM), an autophagy-related protein, has been shown to be in association with inflammatory and infection disease. IRGMs coordinate multiple classes of effectors, including SNARE and BLOC adaptors, autophagy, and lipid droplet proteins, to promote cell-autonomous immunity to intracellular pathogens occupying different vacuolar habitats. IRGM can efficiently induce autophagy to control Mtb infection.[7]

IRGM (syn: LRG47, IFI1) is encoded by the immunity-related GTPase protein family, M gene (IRGM; 5q33.1). IRGM consists of a long first exon encoding 181 amino acids, and 4 shorter putative exons that span more than 50 kilobases (kb) downstream of the first exon. A 20.1 kb upstream deletion polymorphism of IRGM has been found as an increased risk of developing Crohn disease in Caucasians. Intemann CD and colleagues first reported that IRGM polymorphism was related to tuberculosis susceptibility and indicated that rs9637876 (261TT) was significantly associated with protection from TB caused by Mtb, but not by *Mycobacterium africanum*/*Mycobacterium bovis*.[8] Recently, IRGM polymorphisms, such as rs10065172, rs4958842, rs4859843, rs4859846, and rs72553867 were reported in several subsequent studies in different human population. However, there were inconsistent results of association between IRGM polymorphism and tuberculosis susceptibility.[9–15]

To comprehensively evaluate association between IRGM polymorphisms and tuberculosis susceptibility, we searched and retrieved all eligible studies and performed this meta-analysis.

2. Materials and methods

This meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance (Supplementary Table S1, http://links.lww.com/MD/B897). No published review protocol existed for the present study.

2.1. Publication search

In accordance with the PRISMA, we searched the database of PubMed, Embase, and Web of Knowledge for articles published until October 14, 2016 (HX and MZ). The following keywords were used in our study as search strategy: IRGM or LRG47 or "immunity-related GTPase M," and "polymorphism*" or "variant*" or "genetic" or "mutant*," and combined with "tuberculosis." No publication language restrictions were imposed. In addition, the references of selected articles were also checked to identify additional potential studies. The detailed search strategy of this study is presented in Supplementary Table S2, http://links.lww.com/MD/B897.

2.2. Inclusion and exclusion criteria

The inclusion criteria of our study were as follows: studies evaluating associations between IRGM polymorphisms and tuberculosis susceptibility, case-control study, genotype distributions should be available for estimating an odds ratio (OR) with 95% confidence interval (CI). In addition, studies were excluded if fulfilled the following criteria: not related to IRGM polymorphisms or tuberculosis, the design based on family or sibling pairs, and publications were abstracts, reviews, letters to the editor, or animal studies.

2.3. Data extraction

Two investigators independently examined full manuscripts of all included studies, and extracted relevant data into collection form. We evaluated accuracy of data by comparing collection forms from each investigator. Any disagreement was verified by a third author. The following information was collected from each eligible study: first author's name, year of publication, original country, ethnicity, sample size, genotyping method, age, and genotype frequencies in cases and controls.

2.4. Publication bias

Publication bias was assessed by funnel plot. Both Begg test and Egger linear regression test were used to assess publication bias and $P < .05$ was considered statistically significant.

2.5. Statistical analysis

We tested the Hardy-Weinberg equilibrium (HWE) in control group using the chi-square test. The associations of the IRGM polymorphisms with the risk of tuberculosis were assessed by the pooled ORs with the corresponding 95% CIs under the following genetic models: allele model, additive model, dominant model, and recessive model. The pooled OR was calculated for each study by fixed or random effect model. Subgroup analyses were performed in term of ethnicity. The heterogeneity between the studies was investigated by using Cochrane Q test. I^2 was also used to test the heterogeneity among the included studies. A P value $>.10$ for the Q test indicates a lack of heterogeneity among the studies, then the pooled OR estimate of each study was calculated by the fixed-effects model. Otherwise, the random-effects model was used. Sensitivity analysis was performed by sequentially excluding individual study. Statistical analyses were performed using the RevMan 5.3 software, STATA 12.0 software.

3. Results

3.1. Selection and characteristics of studies

A total of 71 articles were identified in the initial search: 16 from Embase, 22 from PubMed, and 33 from Web of Knowledge. Thirty-three articles were discarded because of duplicate records. After title/abstract and full-text screening, 8 articles including 9 case-control studies were included in this meta-analysis. These eligible studies contained 3780 cases and 4835 controls in total. For the rs10065172 polymorphism, 2084 cases and 3302 controls are available in 5 studies.[8,10,13,14] Three studies reported 603 cases and 694 controls for rs4958842, 613 cases and 694 controls for rs4859843, 540 cases and 694 controls for rs4859846, respectively.[9,12,14] There are also 1036 cases and 1051 controls for rs72553867 in 2 studies.[11,13] The distributions of the IRGM gene polymorphism in control group were consistent with HWE in all studies except 1. The whole study selection process and the detailed information of included studies are displayed in PRISMA flow diagram and Table 1, respectively.

Table 1

Characteristics of the case-control studies included in meta-analysis.

First author	Year	Country	Ethnicity	Genotype distribution (case/control)			HIV infection status	HWE, *P* value/control group
SNP rs10065172				TT	TC	CC		
Intemann CD	2009	Ghana	African	280/675	506/1144	218/491	Negative	.87
King KY	2011	USA	Africa American	61/28	202/65	107/87	Negative	.01
King KY	2011	USA	Caucasian	1/1	36/17	140/92	Negative	.83
Lu Y	2016	China	Asian	51/99	114/236	103/140	Negative	.98
Song JH	2014	Korea	Asian	22/39	96/118	75/70	Negative	.37
SNP rs4958842				AA	AG	GG		
Bahari G	2012	Iran	Asian	20/14	130/136	0/0	Negative	<.01
Che N	2010	China	Asian	30/54	93/124	93/97	Negative	.21
Yuan L	2016	China	Asian	32/45	95/112	110/112	Negative	.07
SNP rs4859843				TT	TC	CC		
Bahari G	2012	Iran	Asian	77/9	73/141	0/0	Negative	<.01
Che N	2010	China	Asian	68/82	110/134	38/59	Negative	.75
Yuan L	2016	China	Asian	110/105	101/118	36/46	Negative	.19
SNP rs4859846				TT	TC	CC		
Bahari G	2012	Iran	Asian	138/113	12/35	0/2	Negative	.69
Che N	2010	China	Asian	30/38	97/112	89/125	Negative	.12
Yuan L	2016	China	Asian	181/106	42/114	14/49	Negative	.06
SNP rs72553867				AA	AC	CC		
Songane M	2012	Korea	Asian	1/2	81/91	762/753	Negative	.67
Song JH	2014	Korea	Asian	3/5	70/70	119/130	Negative	.21

HWE = Hardy-Weinberg equilibrium.

3.2. IRGM polymorphisms and tuberculosis susceptibility

Overall, no significant association between IRGM rs10065172 polymorphism and tuberculosis risk was observed under all genetic models. However, whereas latent tuberculosis infection (LTBI) group in 1 study[11,13] was excluded, significant associations were observed in all genetic models, including allele model (OR = 0.86, 95% CI [0.80, 0.94]), additive model (OR = 0.82, 95% CI [0.72, 0.93]), recessive model (OR = 0.77, 95% CI [0.65, 0.90]), and dominant model (OR = 1.19, 95% CI [1.04, 1.37]) (Fig. 1).

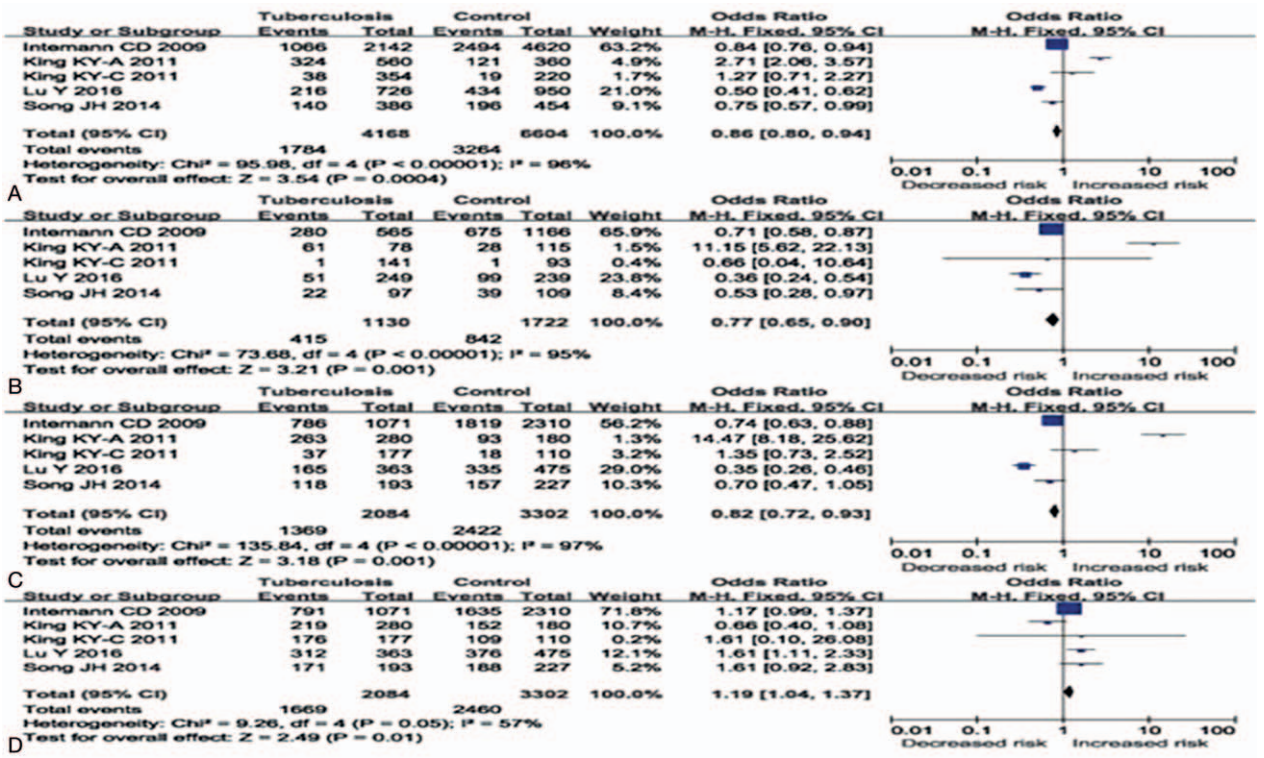

Figure 1. ORs for associations between IRGM rs10065172 polymorphism and tuberculosis risk. (A) T versus C; (B) TT versus CC; (C) CC versus TC+TT; (D) TT versus TC+CC. The sizes of the squares indicate the relative weight of each study. Bars, 95% CI. CI = confidence interval, IRGM = immunity-related GTPase M, OR = odds ratio.

Table 2

Results of the subgroup analyses for the IRGM rs10065172 polymorphism and tuberculosis risk.

Ethnicity	Number of studies	Case/ control	T versus C (allele model)			TT/CC (additive model)			CC versus TC+TT (recessive model)			TT versus TC+CC (dominant model)		
			OR [95% CI] (*P*)	*P*-het	I^2	OR [95% CI] (*P*)	*P*-het	I^2	OR [95% CI] (*P*)	*P*-het	I^2	OR [95% CI] (*P*)	*P*-het	I^2
Asian	2	556/702	0.58[0.49,0.68] (**<.0001**)	.02	80%	0.41[0.29,0.57] (**<.0001**)	.33	0%	0.51[0.41, .63] **<.0001**	<.0001	89%	1.61[1.19, 2.19] **.002**	1	0%
African/ African-American	2	1351/2490	0.98[0.89,1.08] (.68)	<.01	97%	0.94[0.78, 1.13] (.52)	<.01	98%	0.99[0.86, .15] .93	<.0001	98%	1.10[0.94, 1.28] .22	.03	78%

CI = confidence interval, IRGM = immunity-related GTPase M, OR = odds ratio.

Stratified analysis based on race/ethnicity revealed significant associations in all genetic models among Asians, but not for African/African-Americans (Table 2).

Significant associations were also identified in recessive model (OR = 0.35, 95% CI [0.27, 0.45]) and dominant model for rs4958842 (OR = 3.95, 95% CI [2.87, 5.43]), allele model (OR = 0.72, 95% CI [0.61, 0.84]) (Fig. 2), and recessive model (OR = 0.56, 95% CI [0.45, 0.70]) for rs4859843 (Fig. 3) and all genetic models for rs4859846 (Fig. 4), including allelic model (OR = 0.58, 95% CI [0.48, 0.71]), additive model (OR = 0.50, 95% CI [0.34, 0.74]), recessive model (OR = 0.43, 95% CI [0.33, 0.57]), and dominant model (OR = 1.49, 95% CI [1.10, 2.02]).

However, no significant associations between IRGM rs72553867 polymorphism and tuberculosis risk were identified.

3.3. IRGM haplotype and tuberculosis susceptibility

Haplotype constructed with 3 polymorphisms rs4958842, rs4958843, and rs4958846 were reported in 2 studies.[9,15] Significant association was found between ACC haplotype and tuberculosis susceptibility, but not GTT haplotype (Table 3).

3.4. Sensitivity analysis

We performed a sensitivity analysis by sequentially excluding individual study. Overall, statistically similar results were obtained after sequentially excluding each study, which support the reliability of our meta-analysis results.

3.5. Publication bias

For rs10065172 polymorphism, the shape of funnel plot revealed asymmetry to some extent in allelic model (Fig. 5). However, no publication bias was found in both Begg test (*P* value, .462) and Egger linear regression test (*P* value, .405). In addition, publication bias was detected in allele model and additive model of rs4859843 by Egger test and Begg test (Supplementary Table S3, http://links.lww.com/MD/B897).

4. Discussion

Tuberculosis has been recognized as a global public health emergency since 1993,[16] especially in the developing countries, including India, China, Indonesia, Pakistan, Nigeria, and South

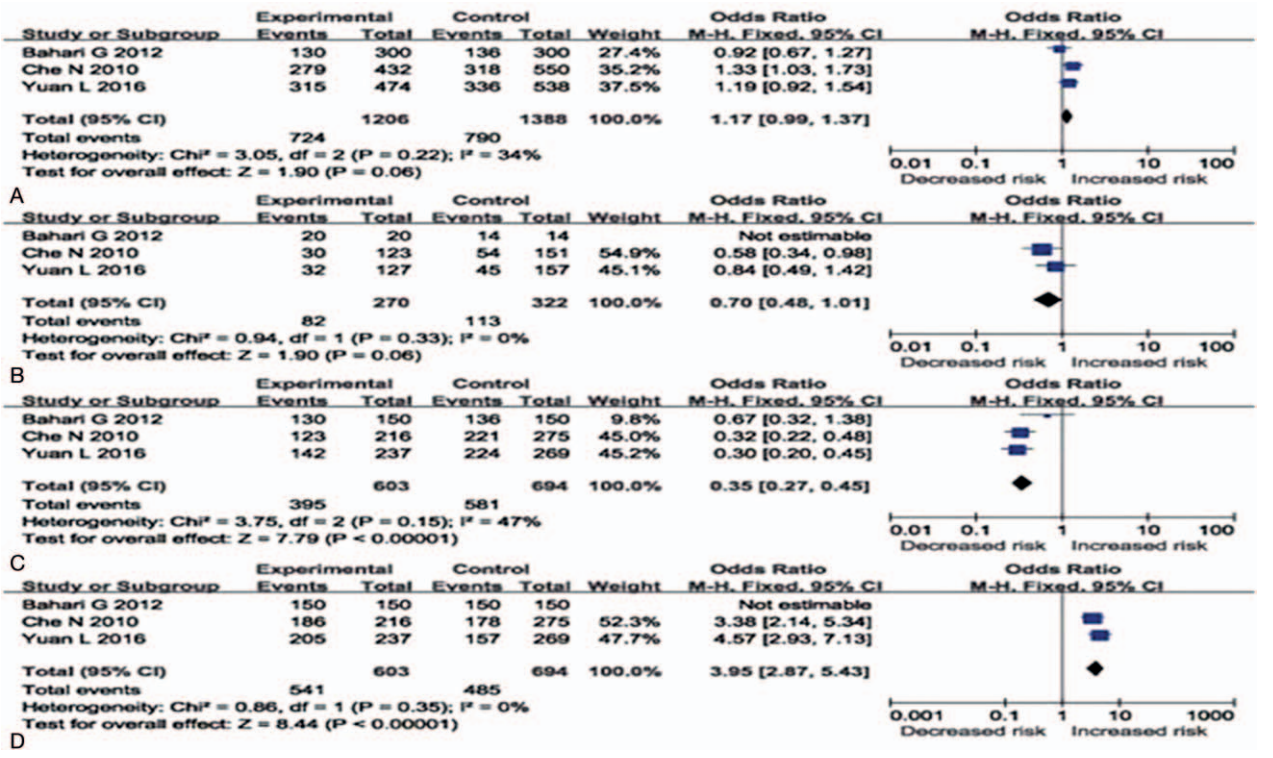

Figure 2. ORs for associations between IRGM rs4958842 polymorphism and tuberculosis risk. (A) A versus G; (B) AA versus GG; (C) AA versus AG+GG; and (D) GG versus AG+AA. The sizes of the squares indicate the relative weight of each study. Bars, 95% CI. CI = confidence interval, IRGM = immunity-related GTPase M, OR = odds ratio.

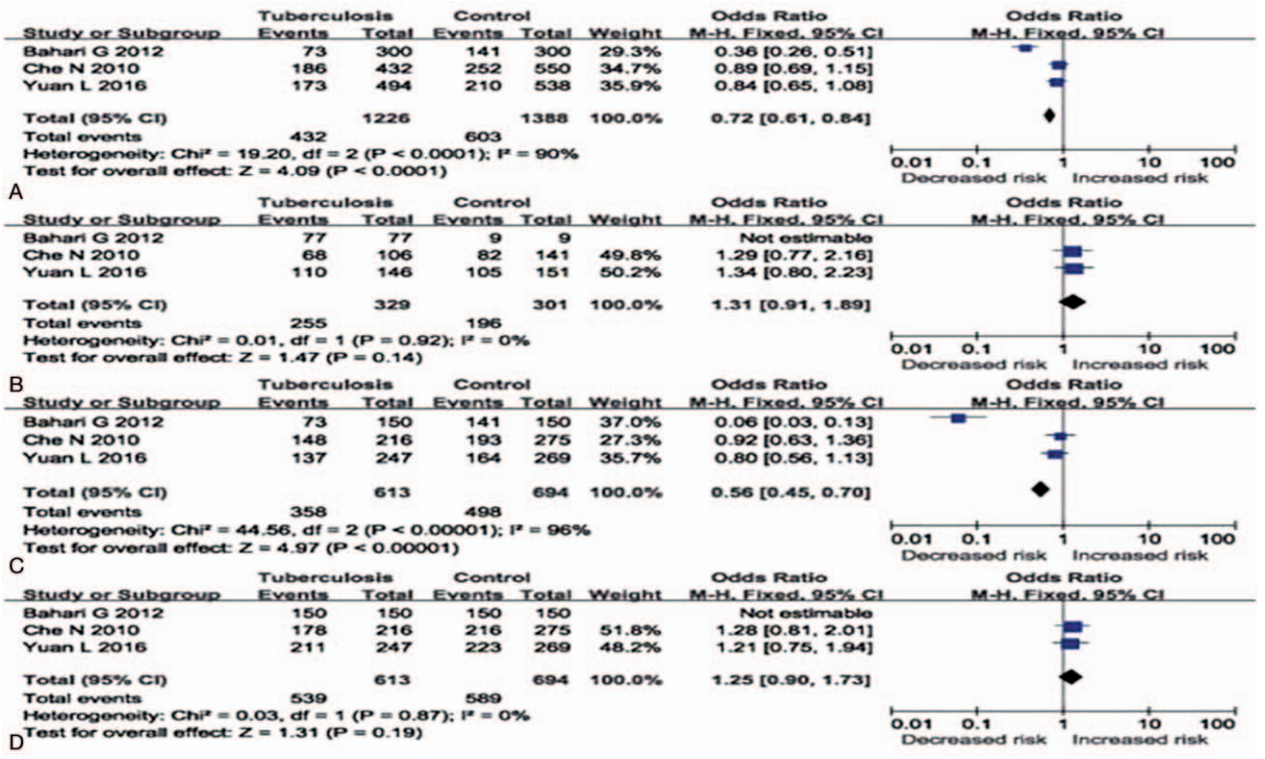

Figure 3. ORs for associations between IRGM rs4859843 polymorphism and tuberculosis risk. (A) T versus C; (B) TT versus CC; (C) CC versus TC+TT; and (D) TT versus TC+CC. The sizes of the squares indicate the relative weight of each study. Bars, 95% CI. CI = confidence interval, IRGM = immunity-related GTPase M, OR = odds ratio.

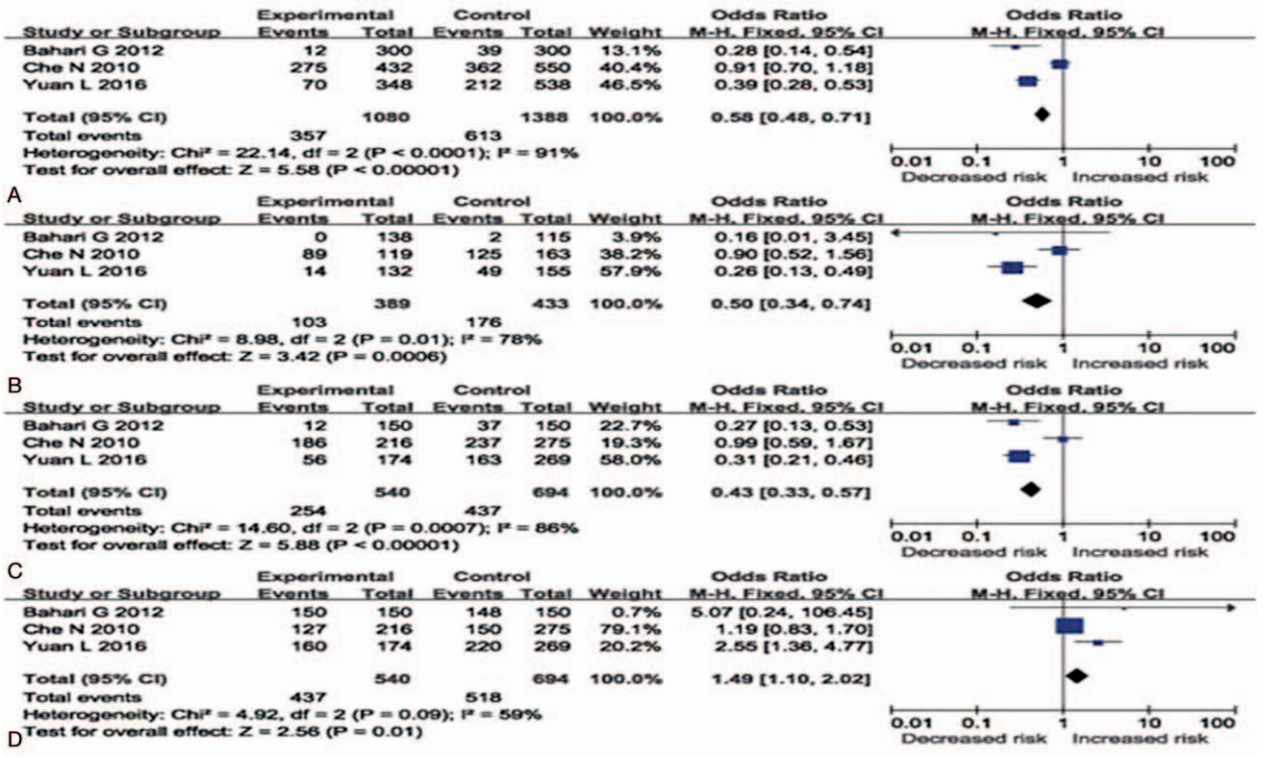

Figure 4. ORs for associations between IRGM rs4859846 polymorphism and tuberculosis risk. (A) T versus C; (B) TT versus CC; (C) CC versus TC+TT; and (D) TT versus TC+CC. The sizes of the squares indicate the relative weight of each study. Bars, 95% CI. CI = confidence interval, IRGM = immunity-related GTPase M, OR = odds ratio.

Table 3

Results of the pooled analyses for other IRGM haplotype and tuberculosis risk.

Variable	Number of studies	Case/control	OR [95% CI] (*P*)	*P*-het	I^2
ACC	2	193/415	0.44 [0.36, 0.54] <**.0001**	<.0001	98%
GTT	2	435/486	1.12 [0.94, 1.34] .22	.96	0%

Haplotype constructed with 3 polymorphisms rs4958842, rs4958843, and rs4958846. CI = confidence interval, IRGM = immunity-related GTPase M, OR = odds ratio.

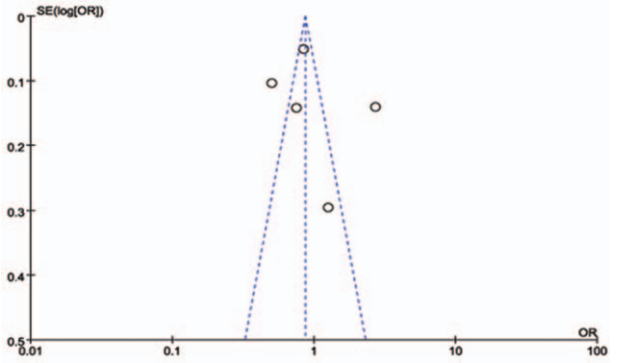

Figure 5. Funnel plot of publication bias for IRGM rs10065172 polymorphism under allele model. Funnel plot with pseudo 95% confidence limits was used. IRGM = immunity-related GTPase M.

Africa. Despite the enormous progress achieved in recent studies, the reason why only a part of the subjects infected with Mtb develops into clinical disease is unknown. Epidemiologic and linkage studies suggest that genetic factors are implicated in the pathogenesis of TB. Cell autonomous immunity is the important mechanism for host against Mtb. Recent progress in the genetic variations involved in the cell-autonomous immunity pathway has advanced understanding the host response to Mtb infection and disease pathogenesis. IRGM, as cell-autonomous immunity-related gene, plays efficient role in controlling Mtb infection. Since the first reports investigating IRGM polymorphisms and tuberculosis susceptibility published in 2009,[8] further studies were conducted in different ethnic groups recently and somehow obtained inconsistent results.

Our meta-analysis enrolled 9 case-control studies containing 3780 cases and 4835 controls to evaluate the association between IRGM polymorphisms and tuberculosis susceptibility. For rs10065172 polymorphism, no significant association was observed under all genetic models whereas LTBI group in 1 study was included. However, after excluding LTBI group, significant associations were found in all genetic models. This suggests that IRGM rs10065172 polymorphism might be associated with disease status of tuberculosis. Stratified analysis based on race/ethnicity show significant associations in all genetic models among Asians. In addition, meta-analysis revealed significant associations between rs4958842, rs4859843, and rs4859846 polymorphism with tuberculosis. Haplotype ACC constructed with rs4958842, rs4958843, and rs4958846 is associated with decreased risk of tuberculosis. However, rs72553867 polymorphism was not found to be associated with tuberculosis susceptibility. Publication bias was detected in allele model and additive model of rs4859843 by Egger test. However, sensitivity analysis indicates the reliability of our meta-analysis, as no single study significantly altered the overall results.

At an individual cell level, host possess the ability to control infection and restrict pathogen replication in a cell-intrinsic manner, which is often referred to as cell-autonomous immunity.[17,18] Recent work demonstrates that induction of autophagy is an effective mechanism to enhance intracellular killing of Mtb in macrophages, and inhibition of this process by pathogen is important for its survival.[19] Some potential disease-associated genetic variants, especially autophagy-related genes, that may predispose to tuberculosis have recently been identified.[19,20] IRGM, one of the IFN-inducible GTPase superfamily, is shown to be involved in the regulation of autophagy[7] and plays an inhibitory effect on the replication of Mtb.[21] Previously, some studies have indicated that IRGM polymorphisms is associated with Crohn disease susceptibility,[22–27] though other studies report no such association.[28,29] To date, studies performed in different human population regarding IRGM polymorphism and tuberculosis susceptibility have yielded inconsistent results. Our meta-analysis results demonstrate significant associations between IRGM polymorphisms and tuberculosis risk for rs10065172, rs4958842, rs4859843, and rs4859846 after excluding LTBI patients.

The strengths of current meta-analysis could be listed as follows. First, to our knowledge, this is the first study aimed to clarify the inexplicit association between IRGM polymorphisms and tuberculosis susceptibility in a meta-analysis manner. Second, HIV tests were performed in all included case-control study. Only those HIV negative tuberculosis patients without immunosuppressive condition were recruited, which excluded the possibility that patient status are confounding factors of tuberculosis susceptibility.

There are some limitations in the present meta-analysis. First, only a small number of studies were found and included in our meta-analysis. Second, studies included in our meta-analysis were mainly conducted in Asian populations. This result should be interpreted with care, since the association found in the Asian population was supported by 5 studies from only 4 publications, which is far from sufficient. Third, gene-gene, gene and environmental factors interaction may have influenced tuberculosis susceptibility. Fourth, deviation from HWE may affect meta-analysis conclusions. However, the results were not significantly altered while excluding study inconsistent with HWE. Fifth, it is worth noting that not all patients are pulmonary tuberculosis, with a small proportion of patients diagnosed with tuberculous pleurisy[9] and extrapulmonary TB.[10] Therefore, the inclusion and exclusion criteria must be specific and comprehensive and should be strictly carried out in the future research.

In summary, the current meta-analysis suggests that IRGM rs10065172, rs4958842, rs4859843, and rs4859846 were associated with a decreased risk of tuberculosis in Asian

populations, whereas rs72553867 was not associated with tuberculosis risk. However, the associations found in Asian populations are needed to be confirmed in more studies. In addition, further researches are warranted to investigate the relations between latent TB infection and IRGM polymorphisms.

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